claims 75 and 77 can be found at section 5.4.2 at page 31 and section 6.1.4 at page 40. Support for claim 76 can be found at page 3, lines 11-16.

II Priority

The specification has been amended to reflect that the present application claims priority to U.S. application Serial No. 08/153,397, filed on November 16, 1993, which is now United States Patent No. 6,051,397.

III Amendments relating to Sequence Listing

The examiner objected to the specification because sequences are disclosed in Figures 1, 3, and 4 without the required reference to their specific sequence identifiers. The examiner states that "this can be resolved by adding a reference [to sequence identifiers] to the Figures or the Brief Description of the Drawings."

Applicants have amended the Brief Description of the Drawings to indicate that the "human MCK-10 nucleotide sequence" and "amino acid sequence" disclosed in the legend of Figures 1A, 1B, and 1C, at page 4, lines 22-23, refer to "SEQ ID NO. 1" and "SEQ ID NO. 2," respectively. Similarly, "(SEQ ID NO. 3)" and "(SEQ ID NO. 4)" have been inserted after the human CCK-2 nucleotide sequence and amino acid sequence respectively, at page 4, line 34. Likewise, the legend for Figure 4A at page 5, now recites "shared sequence homology between MCK-10 (SEQ ID NO. 2) and CCK-2 (SEQ ID NO. 4)."

The examiner also required that "SEQ ID NO. 2" be inserted after "SEQ ID NO. 1" at page 8, line 30. Applicants have amended the sentence accordingly.

The word "with" has been deleted from line 3, page 11 of the specification, so that the sentence is now appropriately written.

Applicants believe that the defects to the specification are now corrected and kindly request that the examiner withdraw her objections.

IV Summary of the invention

The present invention is directed to a method for modulating the endogenous enzymatic activity of an MCK-10 receptor in a mammal by administering an effective amount of a ligand that affects the enzymatic activity of the receptor.

V Rejections under 35 U.S.C. § 112, first paragraph

The examiner rejected claim 30 as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A. The Examiner's Basis for the Rejection

Specifically, the examiner states that "there is no known ligand which binds to and modulates the enzymatic activity of the receptor, so therefore the disclosure is not enabled for this method." See page 4 of the Office Action. The examiner also alleges that "there is no assay taught which would enable the skilled artisan to determine if a potential ligand administered to a mammal actually modulated the activity of the receptor." See page 4.

The examiner believes that it is not "predictable" what ligand would modulate an MCK-10 receptor. See page 5 of the Office Action. Furthermore, the examiner contends that the specification "does not provide any working examples in which a ligand administered to a mammal will modulate the endogenous activity of the MCK-10 protein, and no guidance as to what a ligand would be." See page 5.

Finally, the examiner states that "the specification has not provided guidance as to why the skilled artisan would want to modulate the activity of the MCK-10 receptor" (emphasis added).

Applicants respectfully disagree with the examiner's rationale and interpretation of the present invention and traverse with the rejection.

B. Claim 30 is enabled

Contrary to the examiner's allegation, claim 30 is enabled. The word "ligand" is well known in the art to mean a molecule that binds to another, such as a receptor. To wit, the AMERICAN HERITAGE DICTIONARY OF THE ENGLISH LANGUAGE, 4th Edition, defines ligand as "an ion, a molecule, or a molecular group that binds to another chemical entity to form a larger complex."

Claim 30 recites a method of modulating the activity of the tyrosine kinase MCK-10 receptor by administering an effective amount of a ligand to the MCK-10 receptor protein.

Applicants teach throughout the application various "ligands" that may bind to an MCK-10 receptor. For instance, applicants state at page 29 of the specification that peptide libraries may be used to "identify peptides that are able to bind to the ligand binding site of a given receptor," and conclude that these peptides "may have therapeutic value in the discovery of pharmaceutical agents that act to inhibit the biological activity of receptors." Indeed, applicants go on to teach how the skilled artisan may identify and isolate such peptides. See pages 29-31.

Applicants also teach that an "antibody" is a ligand, in the sense that an antibody may bind to the MCK-10 receptor. See page 31, section 5.4.2. Applicants specifically teach a variety of antibodies, such as "polyclonal, monoclonal, chimeric, single chain, Fab fragments, and fragments produced by

an Fab expression library (see lines 20-22 of page 31) that may be used to bind to an MCK-10 receptor to modulate the activity of the receptor. Certainly, applicants state that "neutralizing antibodies, i.e., those which compete for the ligand binding site of the receptor are especially preferred for diagnostics and therapeutics." See lines, 23-25 of page 31.

Furthermore, applicants teach how to generate MCK-10-specific antibodies and disclose antisera generated against certain MCK-10 epitopes. See section 6.1.4 of page 40, "Generation of MCK-10 Specific Antibodies." There, applicants teach that they made ligands, i.e., antibodies, to discrete regions of the MCK-10 receptor. Thus, αMCK-10-N was generated against amino acids 26-42 of the MCK-10 receptor; αMCK-10-C to amino acids 902-919; αMCK-10-β to amino acids 309-322; and αMCK-10-C2 to amino acids 893-909.

Thus, applicants provide several examples of ligands that bind to an MCK-10 receptor as required by claim 30. Accordingly, the examiner errs in asserting that there is no known ligand that binds to an MCK-10 receptor.

The examiner also errs in stating that applicant teaches "no assay" to determine if a potential ligand administered to a mammal "actually modulated the activity of the receptor."

Applicants teach, at section 6.2.4 at page 47, the expression of MCK-10 receptor clones and how to measure their ability to phosphorylate tyrosine, as well as how to measure their state of glycosylation by using antibodies raised against the MCK-10 N- and C-termini peptides. See page 48 of the specification.

Finally, the specification makes clear that modulation of MCK-10 receptor is desirable, *inter alia* because modulation via ligands can be useful in treating

diseases such as cancer. See, for example, page 1, lines 13-16 and page 5, lines 1-6.

For all of these reasons, claim 30 is enabled and applicants respectfully request that the examiner withdraw this rejection.

VI Rejections under 35 U.S.C. § 112, second paragraph

The examiner rejected claim 30 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The Examiner's Basis for the Rejection

Specifically, the examiner alleges that "the protein identified as MCK-10 in the instant application has the amino acid sequence shown in SEQ ID NO. 2, but since [claim 30] recites 'the MCK-10 receptor' and does not require any structure, it is considered indefinite." See page 6 of the Office Action.

B. Claim 30 is not indefinite

Applicants have amended claim 30 to recite the sequence identifier (SEQ ID NO. 2) describing the amino acid sequence of the MCK-10 receptor protein used in the claimed invention. Applicants also have amended claim 30 to recite splice variants of MCK-10 (*i.e.*, of SEQ ID NO. 2) as set forth in Figure 2 of the specification. The recitation of an "*MCK-10 receptor comprising the amino acid sequence of SEQ ID NO. 2 or splice variants thereof as set forth in Figure 2*" in claim 30 is well supported by the present specification. For instance, splice sequences are described in the figure legend of Figure 1 and within Figure 2. Applicants teach that MCK-10-2 is the complete sequence of the MCK-10 receptor, but that other receptor variants exist, such as those denoted "MCK-10-1," "MCK-10-3," and "MCK-10-4." The nucleic acid transcript encoding MCK-10-1 contains an additional 111 bp; the nucleic acid

encoding MCK-10-4 contains an additional 18 bp; and the nucleic acid encoding MCK-10-3 contains both the 111 bp and the 18 bp insertions. See page 10, lines 2-6, of the specification.

A "variant" may also relate to "members of the MCK-10 family of receptors tyrosine kinases that are defined, herein, as those receptors demonstrating 80% homology at the amino acid level in substantial stretches of DNA sequences with MCK-10." See page 3, lines 11-16.

Accordingly, applicants believe the amendment obviates the examiner's rejection and kindly request that it be withdrawn.

The examiner stated that "the specification has not provided guidance as to why the skilled artisan would want to modulate the activity of the MCK-10 receptor." Applicants point out the present invention relates to "the use of drugs, in the treatment of disorders, including cancer, by modulating the activity of MCK-10." See lines 13-16 of page 1 of the specification. By modulating the activity of MCK-10, one may modulate the phosphorylation state of various cellular substrates that are involved in the cascade of events that lead to cellular responses such as cell proliferation. See, page 2, lines 29-33.

Furthermore, applicants teach that MCK-10 expression is associated with a variety of cancers. See, for instance, Table 1 and accompanying text at pages 12 – 15 of the specification.

Accordingly, applicants provide ample guidance in the present specification as to why one would want to modulate the activity of MCK-10, namely to modulate and inhibit, for instance, cell proliferation. Accordingly, applicants respectfully request the examiner withdraw this rejection.

VII Conclusion

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Michele M Simkins
Reg No. 34,717

Date Aug 8, 2002

By _____
for Beth A. Burrous
Attorney for Applicant
Registration No. 35,087

FOLEY & LARDNER
Washington Harbour
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5143
Telephone: (202) 672-5475
Facsimile: (202) 672-5399

MARKED-UP VERSION OF THE SPECIFICATION

Please replace the first paragraph under "Brief Description of the Figures" at page 4 with the following paragraph:

Figures 1A, 1B and 1C. Human MCK-10 nucleotide sequence [SEQ ID NO 1] and deduced amino acid sequence [SEQ ID NO 2]. Regions of interest include the signal sequence (amino acids (aa) 1-18); the Discoidin I-like domain (aa 31-185); the transmembrane region (aa 417-439); the alternatively spliced sequence I (aa 505-541); the alternatively spliced sequence II (aa 666-671); and the peptide antibody recognition sequences: NTα:aa 25-42, NTβ:aa 309-321, CTβ:aa 902-919.

Please replace the third paragraph under "Brief Description of the Figures" at page 4 with the following paragraph:

Figures 3A, 3B, 3C and 3D. Human CCK-2 nucleotide sequence [SEQ ID NO 3] and deduced amino acid sequence [SEQ ID NO 4].

Please replace the first paragraph of page 5 with the following paragraph:

Figure 4A. Shared sequence homology between MCK-10 [SEQ ID NO 2] and CCK-2 [SEQ ID NO 4].

MARKED-UP VERSION OF THE CLAIMS

30. A method of modulating the endogenous enzymatic activity of the tyrosine kinase MCK-10 receptor comprising the amino acid sequence of SEQ ID NO. 2 or splice variants thereof as set forth in Figure 2 in a mammal comprising administering to the mammal an effective amount of a ligand to the MCK-10 receptor protein to modulate the enzymatic activity.